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Review

Human papillomaviruses and cancer

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ABSTRACT

Human papillomaviruses (HPV) are small oncogenic DNA viruses of which more than 200 types have been identified to date. A small subset of these is etiologically linked to the development of anogenital malignancies such as cervical cancer. In addition, recent studies established a causative relationship between these high-risk HPV types and tonsillar and oropharyngeal cancer. Clinical management of cervical cancer and head and neck squamous cell carcinomas (HNSCCs) is largely standardized and involves surgical removal of the tumor tissue as well as adjuvant chemoradiation therapy. Notably, the response to therapeutic intervention of HPV-positive HNSCCs has been found to be better as compared to HPV-negative tumors. Although the existing HPV vaccine is solely licensed for the prevention of cervical cancer, it might also have prophylactic potential for the development of high-risk HPV-associated HNSCCs. Another group of viruses, which belongs to the beta-HPV subgroup, has been implicated in nonmelanoma skin cancer, however, the etiology remains to be established. Treatment of HPV-induced nonmelanoma skin cancer is based on local excision. However, topically applied immune-modulating substances represent non-surgical alternatives for the management of smaller cutaneous tumors. In this review we present the current knowledge of the role of HPV in cancer development and discuss clinical management options as well as targets for the development of future intervention therapies.

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Papillomaviruses (PVs) are commonly known to cause benign papillomas as well as epithelial malignancies. PVs are small non-enveloped viruses with a diameter of approximately 55 nm and a double-stranded circular DNA genome comprising almost 8000 nucleotide base pairs. The genome is arranged into the upstream regulatory region (URR) and nine to ten open reading frames (ORFs) encoding the viral early and late genes. Late gene expression produces the structural proteins L1 and L2, which assemble into the viral capsid structure, whereas early gene activity translates into the regulatory proteins E1–E8. PVs generally infect keratinocytes within the basal layer of stratified epithelia by gaining access through wounds within the skin and mucosa. Initial attachment to the cell surface has largely been attributed to rely on heparan sulfate proteoglycans [36]. Subsequent conformational changes within L2 result in furin-dependent cleavage of its N-terminal sequence [65]. The current model of cellular entry involves a novel actin-dependent, but clathrin-, cavoelin-, cholesterol- and dynamin-independent pathway related to macropinocytosis [20,71]. Woodham et al. suggest a ligand-induced mechanism in which pre-entry binding of the capsid proteins to integrins may activate signaling cascades that recruit the annexin A2 heterodimer to the cell membrane, which then facilitates internalization of the virus [84]. Viral entry and posterior replication are largely contingent on keratinocyte differentiation.

Human papillomaviruses (HPV) are classified depending on their tissue tropism. Alpha-HPVs infect mucosal tissue whereas beta-, gamma-, nu- and mu-subtypes infect cutaneous sites [17] (see http://pave.niaid.nih.gov for detailed phylogeny). In addition, mucosal HPVs are distinguished by their potential to cause malignant progression. Low-risk HPVs include HPV 6, 11, 40, 42, 43, 44 54, 61, 70, 72 and 81 [62] which can cause low-grade lesions such as condylomas and benign cervical lesions and are rarely found in malignancies [83]. High-risk HPVs including HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66 gained notoriety by being the primary causative agents of cervical carcinoma [14,72].

Alpha-HPV-associated cancer development and therapy

Each year, 0.5 million new cases of cervical cancer are reported with 274,000 associated deaths worldwide [5]. Certain high-risk HPV types, recognized as class I carcinogens by the World Health Organization, are necessary risk factors for the development of cervical cancer [14,39,72]. Early stages (I–IIa) of cervical cancer can be

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treated rather successfully, but locally advanced cancers are characterized by high recurrence rates and a poor prognosis. The standard therapy of locally advanced cervical cancer is a combination of radiotherapy and cisplatin-based chemotherapy with an overall 5-year survival of less than 50%. Patients with stage IV or recurrent cervical cancer treated with cisplatin alone or in combination with topotecan only have a median survival of less than one year [57]. Despite widespread screening for cervical cancer, this disease continues to claim large numbers of lives, particularly among medically underserved populations of women. In addition to cervical carcinoma, high-risk HPVs were found in 26% of head and neck squamous cell carcinomas (HNSCCs) despite the main risk factors being tobacco, alcohol, poor oral hygiene and genetic pre-disposition [44]. It has previously been shown that patients suffering from alcohol- or tobacco-induced HNSCC are at reduced risk of simultaneously contracting HPV-based HNSCC [4,15]. This may be explained by a recent finding that increased levels of the annexin A2 ligand, secretory leukocyte protease inhibitor (SLPI), are typical for tumors induced by smoking [28]. High expression of SLPI in turn inhibits annexin A2, which is essential for viral entry into the host cell [84].

Within the heterogeneous group of HNSCCs, almost 70% of all tonsillar and oropharyngeal carcinoma cases are HPV-positive in economically developed countries [43,52,66]. Regardless of this knowledge there is no screening routine available in order to detect early HPV lesions in the tonsils and oropharynx. Clinical management is largely standardized across the HPV-positive and -negative tumor types and stages of progression. Treatment of stage I and II oropharyngeal cancers usually involves surgery accompanied by radiotherapy. More locally advanced cancers are surgically removed and treated by chemoradiation therapy [51]. It is generally accepted that HPV-positive HNSCCs have a significantly better prognosis as compared to HPV-negative tumors. Patients with HPV-positive tumor status who do not consume tobacco or alcohol presented with a reportedly higher survival rate probably due to increased sensitivity to chemo- and radiotherapy [52]. Several studies show that young individuals seem to be at greater risk for developing HPV-positive tonsillar or oropharyngeal cancers [11,27], with one study reporting a higher percentage of cases in young men [27]. The young age of the risk group may be a result of changes in sexual behavior such as earlier onset of sexual activity and increased oral practices. These patients also exert better responses to intervention therapy and have fewer recurrences as compared to age-matched patients with HPV-negative HNSCCs [52].

Since 2006 two recombinant vaccines against human papillomavirus types 6, 11, 16, and 18 are available. Although this is an important step in the battle against cervical cancer, the viral types for which these vaccines provide protection are responsible for only 70% of the cases of cervical cancer [39]. However, it has been shown that the vaccines confer cross protection against HPV types 31, 45 and 52 (reviewed by [6]). It is worth noting that in more than 95% of HPV-positive tonsillar and oropharygeal cancers the high-risk types HPV 16 and 18 were detected [44] and a prophylactic vaccine regime may be the key in preventing HPV-based head and neck cancers. Currently there are no data available evaluating the efficacy of HPV-vaccination for preventing oral cancers. Even though vaccination may prevent HPV-associated cancers, previous assumption was that it will provide no protection for individuals who already have been exposed to high-risk HPV types. However, recent research demonstrates a 67% efficacy of the quadrivalent vaccine Gardasil® in seropositive, but HPV DNA-negative women aged 24–45 years [10]. Nevertheless, the need for significant advances in the diagnosis and treatment of HPV-dependent cancers will persist.

By better understanding the course of high-risk HPV infection, new approaches for clinical management of both cervical carcinoma and HNSCCs may be discovered. The normal productive PV life cycle is tightly linked to keratinocyte differentiation where the genome undergoes episomal replication generating infectious viral particles. Persistent infection with high-risk types, however, may lead to the integration of viral DNA into the host cell genome, which is accompanied by a deletion of the genes encoding the viral replication regulators E1 and E2. The expression of E2 proteins has been described to repress the transcription of the viral oncogenes E6 and E7 [21]. Therefore, loss of the E2 region during integration may lead to the constitutive activation of both oncogenes thereby fostering carcinogenesis. However, recent reports demonstrate that in approximately 35% of cervical cancer patients full-length viral genomes are present and actively transcribed raising the possibility of E2-expression in addition to E6 and E7-proteins within cervical cancer cells [40,50]. E6 and E7 of HPV16 and 18 interact with a large number of host cell proteins in order to manipulate cell proliferation, senescence and apoptosis (Fig. 1). The E6-proteins of high-risk HPV interact with the p53 tumor suppressor and induce its proteolytic degradation [70]. In addition, HPV 16 E6-protein has been shown to induce telomerase activity [41]. Both functions as well as E6-induced transcriptional changes in HPV-positive cells were reported to be dependent on the ubiquitin-ligase E6-associated protein (E6AP) [69]. Finally, E6-proteins of high-risk HPVs share a conserved C-terminal domain, which mediates its interaction with PDZ (PSD-95, Dlg, Zo-1) domain-containing proteins such as hDlg [38,48], MAGI-1 [26], hScrib [63], MUPP1 [47] and PTPN3 [35] which are involved in epithelial cell polarity [54,59]. E7 interacts with the retinoblastoma-family tumor suppressor proteins pRb [24,61,73], p107 [46] as well as p130 [16] and disrupts their interaction with E2F transcription factors, resulting in the activation of E2F-dependent gene expression and cell cycle progression [7,53,56]. One of the proteins up-regulated upon pRb degradation is p16, which is encoded by the sequence of the CDKN2a gene [37]. An accumulation of p16 was reported in HPV-positive cancers and serves as a prognostic marker for intervention therapy responses [42,55]. Expression of E6 and E7 transcripts is controlled by both cellular and viral transcription factors. Interestingly, E6 and E7 also act as potent mitotic mutators, thereby increasing the occurrence of mutations that contribute to carcinogenic progression (reviewed in [54]). These multiple interactions with important cellular pathways of the host cell may represent potential targets for developing specific therapeutic alternatives for HPV-based cancer treatment. Other intervention therapy approaches may arise from the fact that normal cells and tumor cells markedly differ in their energy metabolism. When glucose is metabolized in normal cells in the presence of adequate oxygen, the process results in complete oxidation of glucose and involves cytoplasmic glycolysis as well as mitochondrial citric acid cycle and electron transport chain/oxidative phosphorylation. In contrast, tumor cells rely mostly on the conversion of glucose into lactate rather than mitochondrial oxidation for energy production. The mitochondrial function is suppressed in most tumor cells even though oxygen is available [33]. In agreement with these findings in virally transformed cells, HPV-induced oncogenic transformation of cervical epithelium is associated with increased expression of the glucose transporter GLUT1 [67]. Some studies have shown that more aggressive tumors have a greater demand for metabolic energy and hence for glucose. Accordingly, the expression level of GLUT1 correlates reciprocally with the survival of cancer patients [82]. A recent study has demonstrated a role for the sodium-coupled glucose transporter SGLT1 in epithelial cancers [82]. The levels of SGLT1 protein and its transport activity are elevated in malignant epithelial cell lines by the co-expression of EGFR, which stabilizes SGLT1 within the membrane. Overexpression of EGFR is frequent in cervical cancer cells [25] as well as HPV-positive head and neck tumors [45], providing a basis for exploiting the EGF

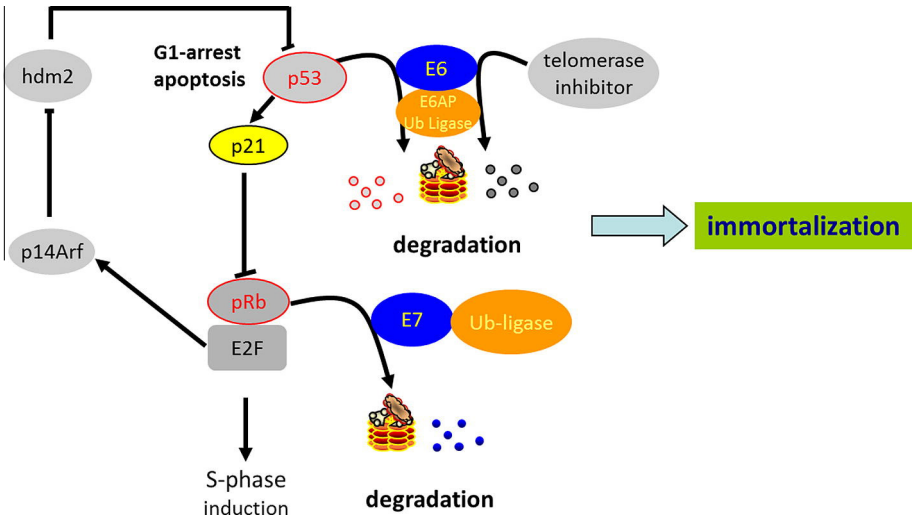

Fig. 1. Interference of high-risk genital α-HPV E6 and E7 proteins with the host cell cycle.

pathway as a therapeutic target. The regulation of SGLT1 by EGFR might have immense clinical relevance. Small molecule tyrosine kinase inhibitors show little efficacy in the treatment of cancers with high EGFR expression [25]. In contrast, antibodies directed against the extracellular domain of EGFR may have the ability to block the interaction of EGFR with SGLT1, thus blocking SGLT1-mediated glucose entry into EGFR-positive cancer cells and eventually causing cell death [19]. Increased glucose uptake, however, causes a significant problem for the cell by decreasing the cellular pH and potentially compromising cell survival unless other mechanisms counteract cellular acidification. The growth factor-sensitive sodium-proton exchanger NHE1 is a significant mediator of pH regulation in tumor cells (Fig. 2). This transporter pumps H^+ out of the cells, coupled to a transmembrane Na^+ gradient. The activity of NHE1 is induced in several cancers by growth factors such as EGF and, more importantly, by HPV oncoproteins. Cellular transformation by the E7-protein was shown to require the stimulation of NHE1 [9]. The regulatory factor of NHE1, called NHERF1, recruits membrane receptors, transporters and cytoplasmic signaling proteins into functional complexes, thereby increasing NHE1 activity. It was shown that HPV16 E6 degrades NHERF1 by a process requiring the E6 PDZ domain and the ubiquitin ligase E6AP [2]. Consistent with a manipulation of the cellular metabolism by HPV oncoproteins, we have recently found that the E6-protein activates SGLT1 [49] and that PV-induced tumors in animals display a high glucose uptake as shown by *in vivo* imaging techniques (Probst et al. submitted for publication).

Beta-HPV-associated cancer development and therapy

A number of reports demonstrated that various nonmelanoma skin cancer (NMSC) types contain DNA of beta (β)-HPV species 2 [22]. While it is generally accepted that high-risk HPVs are causative for cervical, anogenital and some oropharyngeal cancers, the etiological association of HPV and cutaneous cancers has not been clearly demonstrated. Skin cancers based on HPV include cutaneous squamous cell carcinoma (cuSCC). Among the risk groups are patients receiving immunosuppressive treatment or individuals with acquired immunodeficiency syndrome who are generally more susceptible to opportunistic infections. In addition, patients presenting with epidermodysplasia verruciformis (EV) are at risk of developing HPV-associated cutaneous malignancies. EV is a rare genetically inherited skin disorder which is characterized by an increased susceptibility of the skin to certain β-HPV types. These include HPV 5, 8, 9, 12, 14, 15, 17, 19–25, 36–38, 46, 47, 49 and 50 and have been termed "EV-types" due to their increased occurrence in EV patients [13]. At least 30% of the affected individuals will develop invasive squamous cell carcinomas and about 90% of these tumors are associated with the HPV types 5 and 8 as high copy numbers have been detected within tumor tissue [18]. Although a role of HPV in cutaneous cancer development seems likely [3,31], HPV infection is not however sufficient to induce cancerogenesis in EV patients. The vast majority of tumors develop on sun-exposed skin and a role of ultraviolet (UV) radiation has been demonstrated in a number of reports. Most recently Wallace and co-workers showed that the HPV 5 and 8 E6 protein sensitizes the cells to UVB exposure by disrupting the DNA double-strand break repair mechanisms [81]. In addition, previous work showed that the E6 protein of HPV types 1, 8 and 16 directly binds the DNA repair protein XRCC1, which ultimately leads to a reduction of the base excision repair pathway efficiency [32]. In line with the fact that cutaneous HPV types are ubiquitously present on the human skin, the impaired DNA repair activity may explain why immunocompetent individuals are at risk of developing β-HPV-associated

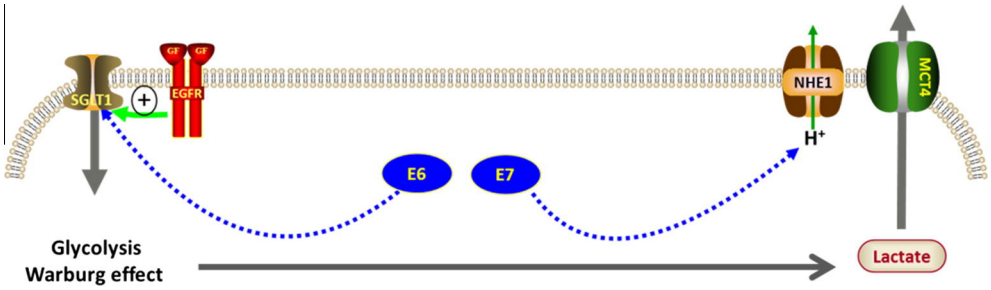

Fig. 2. Effect of high-risk α-HPV E6 and E7 on the glucose metabolism.

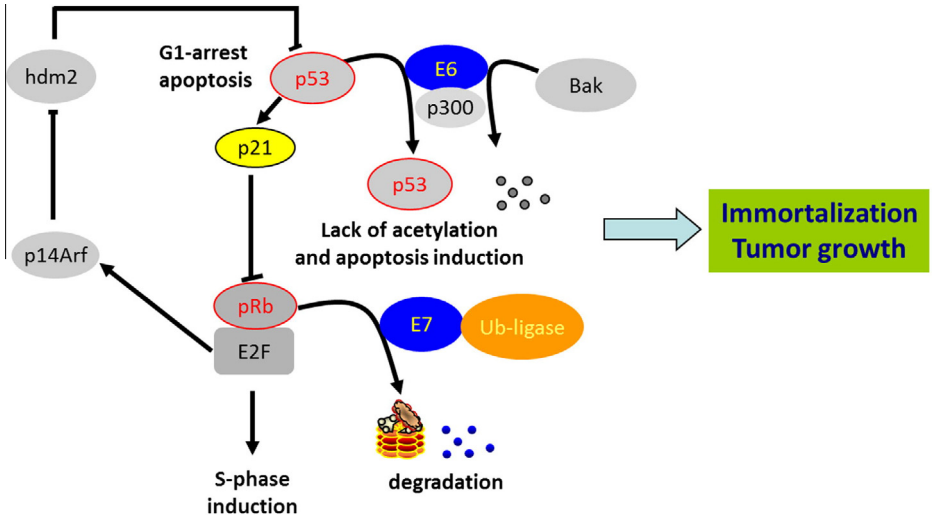

Fig. 3. Interference of high-risk cutaneous β-HPV E6 and E7 proteins with the host cell cycle.

NMSCs upon local or systemic immunosuppression [22]. NMSC is the most frequent human malignancy worldwide and its incidence rate is continually rising. Clinical management of NMSC usually involves surgical removal of the tumor tissue. Radiation therapy may be employed as a primary or adjuvant treatment option of persistent or recurrent advanced cancer lesions. More superficial cutaneous tumors may be treated by topical application of chemotherapeutic agents, laser therapy or intra-lesional interferon. Alternatively, novel immune-modulating agents such as imiquimod and photodynamic therapy have also been proven effective [64]. Although surgery continues to be the most efficient treatment option, the search for less invasive therapies is on-going. A great advantage of researching novel intervention points in HPV-associated NMSC is the availability of a well-established animal model system. Infection of New Zealand White rabbits with the cottontail rabbit papillomavirus (CRPV) results in papilloma development on the skin of the animals within 4–6 weeks and invasive malignant progression after 6–12 months post-infection [34,76,85]. Using this *in vivo* system, the histone acetyltransferase p300 was recently identified as a CRPV and β2-HPV 38 E6 interacting factor [60] similar to the α-HPV E6 [86] rendering it a central cellular target for both α- and β-HPV. This interaction was shown to disrupt p53 induced apoptosis [60]. However, unlike high-risk HPV E6, which directly associates with p53 causing its degradation and low-risk HPV E6 which binds p300 thereby blocking p53 acetylation necessary for p53 stability, β-E6 appears to directly cause p300 degradation (Fig. 3). Recent publications of the group of Denise Galloway have depicted this mechanism and its consequences in more detail and found that p300 is subjected to proteasomal degradation upon HPV 5, 8 and 38 E6 binding, which prevents its association with AKT [29]. In uninfected cells AKT would phosphorylate p300 which stabilizes the protein. Further research revealed that the downstream PI3 kinase family member ATR fails to phosphorylate p53 upon p300 degradation, which increases the UVB sensitivity of infected cells and allows cell cycling despite damaged DNA [80]. In addition, β-HPV 38 E6 has been shown to indirectly reduce p53 protein levels by accumulating the p53 inhibitor deltaNp73 [1]. Another difference between α- and β-E6 is the fact that unlike high-risk α-HPV E6, β-HPV E6 does not contain a PDZ domain and therefore cannot associate with PDZ-binding proteins. However, both α- and β-E6 proteins share functions such as the activation of the ribonucleoprotein telomerase [8,41] and the interaction with host proteins including the E3 ubiquitin ligase E6AP [8,30,69] and Bak [77–79] which plays a critical role in UV-induced apoptosis. Several β-E6 proteins target Bak for proteasomal degradation, thus preventing apoptosis in UV-exposed keratinocytes [79]. The functions exerted by the oncoprotein E7 of cutaneous HPV types are similar to the activities of the mucosal HPV E7 protein [12], which involves binding and degradation of pRB, thus inducing cell cycle progression [73].

Conclusion

Altogether, there are clear functional differences between α- and β-HPV oncologies, and also between high- and low-risk viruses. The role of high-risk HPV types in cervical cancer and in some tonsillar and oropharyngeal tumors has been well studied, in fact most of the knowledge about HPV-dependent oncogenesis originates from the high-risk types HPV 16 and 18. In contrast, the causal relationship between NMSC and β-HPV remains to be further established, but clinical studies are complicated by the abundant presence of a large variety of HPV types on the normal skin. Apart from anogenital, tonsillar and oropharyngeal tumors and nonmelanoma skin cancer, HPV DNA has been detected in various other cancer types including cancers of the lung [75,80], breast [23], brain [68] and bladder [74]. These reports, however, are sparse and with the exception of bladder cancer, most of these tumors were found to be metastases from previously identified cervical or HPV-based head and neck carcinomas. Active transcription of the high-risk HPV types was not observed in any of these cases. The development and application of novel detection methods testing for both α- and β-viruses may reveal the true extent of HPV-associated oncogenesis.

HPV is the most common sexually transmitted disease worldwide and accounts for a significant number of malignancies each year. A widespread vaccination regime would help decrease the burden, HPV infections inflict on public health systems. In addition, the development of novel more targeted intervention therapies is ongoing and promising candidate treatments include for example therapeutic vaccines (reviewed by [58]).

Conflict of Interest

We declare no conflicts of interest.

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